

REMARKS

Applicant acknowledges receipt of an Office Action dated June 24, 2009. In this response, Applicant has amended claims 22-27, 28-29, 31-34, 36, 38, and 41. Support for these amendments can be found, for example, at page 5, line 1–page 7, line 35, page 4, lines 9-19; and the descriptions of Figs. 1-6 of the originally filed specification. Claims 22-41 remain pending in the application.

Applicant respectfully requests reconsideration of the present application in view of the reasons that follow.

Claim Objections

On pages 2-3 of the Office Action, the Office has objected to claims 23-27 and 29-41 for informalities.

Regarding the objection to claims 23-26, Applicant has amended claims 23-26 to refer to the step of determining in vivo distribution of independent claim 22.

Regarding the objection to claim 27, Applicant has amended claim 27 to clarify that the additional features relate to the detectors of claim 22.

Regarding the objection to claim 29, Applicant has amended claim 29 to clarify that the claim feature in question is with respect to “a first detector”.

Regarding the objection to claims 31, 32, 34 and 38, Applicant has amended the claims to clarify its relationship to features of claim 29.

Regarding the objection to claims 33 and 36, Applicant has amended the claims to clarify the recited features.

Regarding the objection to claim 41, Applicant has amended the claim to define NIRF as near infrared fluorescent.

In view of the foregoing, reconsideration and withdrawal of the objections are respectfully requested.

Rejections Under 35 U.S.C. § 103

Background

The subject-matter of the claimed invention is based on the arrangement of imaging detectors of different kinds. The present invention does not relate to detectors for distinct X-ray energies only, nor does it relate to detectors for distinct light colors. As recited in the independent claims, as well as to the very detailed discussions of previous responses of April 13, 2009 and January 7, 2009, two different kinds of detection are recited in the independent claims similar to the following outline:

(a) first detector - bioluminescent/fluorescent markers - the markers provide photons of a first average energy (light)

(b) second detector - radioactive markers - the markers provide photons of a second average energy (radioactive radiation).

The claimed invention is not limited to only detectors for X-ray energies or only detectors for light energies. Rather, it is a concept underlying the claimed invention to combine detectors for radioactive markers with detectors for luminescent markers.

In addition, both kinds of detection do not provide one single luminescence value for measuring clearance of markers. Rather, both kinds of detection provide imaging data, ie. measurements of radiation distributed on a 2D-surface (or even in a 3D-space). In other words, the claimed invention provides a method and apparatus for imaging.

Claims 22 and 28

On pages 3-4 of the Office Action, the Office has rejected claims 22 and 28 under 35 U.S.C. § 103(a) as allegedly being unpatentable over U.S. Patent No. 6, 280,703 to Combs *et al.* (hereafter “Combs”), in view of U.S. Patent No. 4,969,175 to Nelson *et al.* (hereafter “Nelson”). Applicant traverses these rejections for the reasons set forth below.

Combs fails to teach or suggest an imaging method, wherein the imaging method comprises, among other things, “determining in vivo distributions of bioluminescent and/or fluorescent markers and radioactive markers at identical projection angles, wherein the distribution of the bioluminescent and/or fluorescent markers is determined by separate detection of photons having a first average energy, which are emitted by the bioluminescent

and/or fluorescent markers, by at least one first detector and wherein the distribution of the radioactive markers is determined by simultaneous separate detection of photons having a second average energy, which are emitted by the radioactive markers, by at least one second detector, wherein the at least one first detector and the at least one second detector are fixedly arranged in a specific spatial arrangement relative to each other; and wherein the at least one first detector and the at least one second detector are fixedly arranged as a rigid arrangement” (emphasis added), as now recited in independent claims 22 and 28.

For example, Combs is silent with respect to the type of arrangement of the first detector relative to the second, and does not teach or suggest imaging at two different energy levels at the same projection angle.

With respect to the arrangement of detectors, the Office states that “...some determined spatial arrangement would be necessary, especially in the case of simultaneous detection”. However, Applicant submit simultaneous detection of a clearance function requires two detectors to be located at the same object, but does not require two detectors in a fixed arrangement. Such a fixed arrangement is only required if the arrangement of detectors to the object is critical, e.g., for imaging as in the claimed invention, and Combs does not teach or suggest an apparatus used for imaging at all. Instead, Combs is directed to depletion measurements.

The Office has attempted to combine Nelson with Combs, however Applicant submits that Nelson fails to remedy the deficiencies of Combs. For example, Nelson exclusively relates to X-ray imaging. For example, Figures 3a, 3b as well as Figure 6 of Nelson relate to the distinct X-ray photon energies. As can be seen from Figures 1, 2, 4, 5, and 8-16 of Nelson, multilayer X-ray mirrors are used to distinguish the energies. For a person skilled in the art, it is absolutely clear that these mirrors cannot be used for light which is emitted by luminescent or fluorescent substances. In particular, it is physically impossible to use X-ray multilayer mirrors for distinguishing light emitted by luminescence.

Furthermore, Nelson clearly relates to “conventional X-ray tube slit scan systems” as referred to in the lines prior to column 4, line 38. Nelson does not teach or suggest how to combine a X-ray imaging with the simultaneous or alternate imaging of luminescent or fluorescent markers. In particular, the word “light” or any other term relating to light photons, is not given in Nelson. Also, since Nelson relates to the combination of only X-ray

detection of distinct energies, it leads away from the claimed invention. Thus, since Nelson lacks a teaching or suggestion to enable one of ordinary skill in the art to combine with Combs, it appears that the Office has inadvertently, but improperly, relied upon Applicant's disclosure to assemble disparate pieces from the cited references in an attempt to arrive at Applicants claimed invention.

In view of the foregoing, reconsideration and withdrawal of the rejection are respectfully requested.

Claims 23 and 24

On pages 4 of the Office Action, the Office has rejected claims 23 and 24 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Combs in view of Nelson and further in view of U.S. Patent 6,757,554 to Rubinstein *et al.* (hereafter "Rubinstein"). Applicant respectfully traverse this rejection for at least the reasons set forth below.

Rubinstein fails to remedy the deficiencies of Combs and Nelson as described above. For example, Rubinstein fails to teach or suggest "simultaneously determining in vivo distributions of bioluminescent and/or fluorescent markers and radioactive markers at identical projection angles, wherein the distribution of the bioluminescent and/or fluorescent markers is determined by separate detection of photons having a first average energy, which are emitted by the bioluminescent and/or fluorescent markers, by at least one first detector and wherein the distribution of the radioactive markers is determined by simultaneous separate detection of photons having a second average energy, which are emitted by the radioactive markers, by at least one second detector, wherein the at least one first detector and the at least one second detector are fixedly arranged in a specific spatial arrangement relative to each other; and wherein the at least one first detector and the at least one second detector are fixedly arranged as a rigid arrangement", as recited in independent claim 22, from which claims 23 and 24 ultimately depend.

Rubinstein discloses an approach for measuring a dye concentration within an animal. According to column 3, lines 34-53 of Rubinstein, a fluorescent dye indicator dilution is measured using a one-dimensional photodetector, cf. column 5, lines 28-40. Such a photodetector is not capable of imaging. Rather, since only a concentration is to be measured in Rubinstein, only one light intensity is provided by the photodetector. *See* Rubinstein at column 5, lines 41-49. Thus, the approach of Rubinstein, is not compatible with imaging nor

is it related to a distinct wavelength and, in particular, does not relate to light measurements concurrent with X-ray measurements. Instead, Rubinstein merely teaches clearance detection using light only, and, consequently, teaches away from the claimed invention. Further, the device shown in Figure 1 and Figure 3 of Rubinstein is based on laser excitation which is inherently involved with emitting only one light point. Since only one light point is measured in Rubinstein, Applicants submit that the reference teaches away from any imaging methods.

Additionally, if an independent claim is nonobvious under § 103, then any claim depending therefrom is nonobvious. *In re Fine*, 5 USPQ2d 1596 (Fed. Cir. 1988). See MPEP 2143.03. Thus, Applicants submit that claims 23 and 24, each of which ultimately depend from independent claim 22, are also non-obvious at least by virtue of their dependency from claim 22.

In view of the foregoing, reconsideration and withdrawal of the outstanding rejection are respectfully requested.

Claim 25

On pages 4-5 of the Office Action, the Office has rejected claim 25 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Combs in view of Nelson and further in view of U.S. Patent 6,232,107 to Bryan *et al.* (hereafter “Bryan”). Applicants respectfully traverse this rejection for at least the reasons set forth below.

Bryan fails to cure the deficiencies of Combs in view of Nelson. For example, Bryan fails to teach or suggest “simultaneously determining in vivo distributions of bioluminescent and/or fluorescent markers and radioactive markers at identical projection angles, wherein the distribution of the bioluminescent and/or fluorescent markers is determined by separate detection of photons having a first average energy, which are emitted by the bioluminescent and/or fluorescent markers, by at least one first detector and wherein the distribution of the radioactive markers is determined by simultaneous separate detection of photons having a second average energy, which are emitted by the radioactive markers, by at least one second detector, wherein the at least one first detector and the at least one second detector are fixedly arranged in a specific spatial arrangement relative to each other; and wherein the at least one first detector and the at least one second detector are fixedly arranged as a rigid arrangement”, as recited in independent claim 22, from which claim 25 depends.

If an independent claim is nonobvious under § 103, then any claim depending therefrom is nonobvious. *In re Fine*, 5 USPQ2d 1596 (Fed. Cir. 1988). See MPEP 2143.03. Thus, Applicants submit that claim 25, which ultimately depends from independent claim 22, is also non-obvious at least by virtue of their dependency from claim 22.

In view of the foregoing, Applicant reconsideration and withdrawal of the outstanding rejection are respectfully requested.

Claim 26

On pages 4-6 of the Office Action, the Office has rejected claim 25 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Combs in view of Nelson and further in view of U.S. Patent Application Publication 2003/0101466 to Turner (hereafter “Turner”). Applicants respectfully traverse this rejection for at least the reasons set forth below.

Turner fails to cure the deficiencies of Combs in view of Nelson. For example, Turner fails to teach or suggest “simultaneously determining in vivo distributions of bioluminescent and/or fluorescent markers and radioactive markers at identical projection angles, wherein the distribution of the bioluminescent and/or fluorescent markers is determined by separate detection of photons having a first average energy, which are emitted by the bioluminescent and/or fluorescent markers, by at least one first detector and wherein the distribution of the radioactive markers is determined by simultaneous separate detection of photons having a second average energy, which are emitted by the radioactive markers, by at least one second detector, wherein the at least one first detector and the at least one second detector are fixedly arranged in a specific spatial arrangement relative to each other; and wherein the at least one first detector and the at least one second detector are fixedly arranged as a rigid arrangement”, as recited in independent claim 22, from which claim 26 depends.

If an independent claim is nonobvious under § 103, then any claim depending therefrom is nonobvious. *In re Fine*, 5 USPQ2d 1596 (Fed. Cir. 1988). See MPEP 2143.03. Thus, Applicants submit that claim 26, which ultimately depends from independent claim 22, is also non-obvious at least by virtue of their dependency from claim 22.

In view of the foregoing, Applicant reconsideration and withdrawal of the outstanding rejection are respectfully requested.

Claim 27

On pages 4-6 of the Office Action, the Office has rejected claim 25 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Combs in view of Nelson, further in view of Turner, and further in view of U.S. Patent 6,312, 961 to Voirin *et al.* (hereafter “Voirin”). Applicants respectfully traverse this rejection for at least the reasons set forth below.

Voirin fails to cure the deficiencies of Combs in view of Nelson, further in view of Turner. For example, Voirin fails to teach or suggest “simultaneously determining in vivo distributions of bioluminescent and/or fluorescent markers and radioactive markers at identical projection angles, wherein the distribution of the bioluminescent and/or fluorescent markers is determined by separate detection of photons having a first average energy, which are emitted by the bioluminescent and/or fluorescent markers, by at least one first detector and wherein the distribution of the radioactive markers is determined by simultaneous separate detection of photons having a second average energy, which are emitted by the radioactive markers, by at least one second detector, wherein the at least one first detector and the at least one second detector are fixedly arranged in a specific spatial arrangement relative to each other; and wherein the at least one first detector and the at least one second detector are fixedly arranged as a rigid arrangement”, as recited in independent claim 22, from which claim 27 depends.

If an independent claim is nonobvious under § 103, then any claim depending therefrom is nonobvious. *In re Fine*, 5 USPQ2d 1596 (Fed. Cir. 1988). See MPEP 2143.03. Thus, Applicants submit that claim 25, which ultimately depends from independent claim 22, is also non-obvious at least by virtue of their dependency from claim 22.

In view of the foregoing, reconsideration and withdrawal of the outstanding rejection are respectfully requested.

Claims 29 and 30

On pages 4-6 of the Office Action, the Office has rejected claims 29 and 30 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Combs in view of Nelson, further in view of Turner, further in view of Voirin and further in view of Rubinstein. Applicants respectfully traverse this rejection for at least the reasons set forth below.

Combs in view of Nelson, further in view of Turner, further in view of Voirin and further in view of Rubinstein fail to teach or suggest an apparatus for “simultaneously

determining in vivo distributions of bioluminescent and/or fluorescent markers and radioactive markers at identical projection angles, wherein the distribution of the bioluminescent and/or fluorescent markers is determined by separate detection of photons having a first average energy, which are emitted by the bioluminescent and/or fluorescent markers, by at least one first detector and wherein the distribution of the radioactive markers is determined by simultaneous separate detection of photons having a second average energy, which are emitted by the radioactive markers, by at least one second detector, wherein the at least one first detector and the at least one second detector are fixedly arranged in a specific spatial arrangement relative to each other; and wherein the at least one first detector and the at least one second detector are fixedly arranged as a rigid arrangement”, as recited in the method for which the apparatus claim 29 is directed. Claim 30 depends from claim 29.

Combs is silent with respect to the type of arrangement of the first detector relative to the second, and does not teach or suggest imaging at two different energy levels at the same projection angle. Also, Applicant submit that simultaneous detection of a clearance function requires two detectors to be located at the same object, but does not require two detectors in a fixed arrangement. Such a fixed arrangement is only required if the arrangement of detectors to the object is critical, e.g., for imaging as in the claimed invention, and Combs does not teach or suggest an apparatus used for imaging at all. Instead, Combs is directed to depletion measurements.

The Office has attempted to combine Nelson with Combs, however Applicant submits that Nelson fails to remedy the deficiencies of Combs. For example, Nelson exclusively relates to X-ray imaging. Figures 3a, 3b as well as Figure 6 relate to the distinct X-ray photon energies. As can be seen from Figures 1, 2, 4, 5, and 8-16, multilayer X-ray mirrors are used to distinguish the energies. For a person skilled in the art, it is absolutely clear that these mirrors cannot be used for light which is emitted by luminescent or fluorescent substances. In particular, it is physically impossible to use X-ray multilayer mirrors for distinguishing light emitted by luminescence.

Furthermore, Nelson clearly relates to “conventional X-ray tube slit scan systems” as referred to in the lines prior to column 4, line 38. Nelson does not teach or suggest how to combine a X-ray imaging with with the simultaneous or alternate imaging of luminescent or fluorescent markers. In particular, the word “light” or any other term relating to light

photons, is not given in Nelson. Also, since Nelson relates to the combination of only X-ray detection of distinct energies, it leads away from the claimed invention. Thus, Applicants submit that Nelson lacks a teaching or suggestion to enable one of ordinary skill in the art to combine the reference with Combs to arrive at the claimed invention.

Further, Rubinstein discloses an approach for measuring a dye concentration within an animal. According to column 3, lines 34-53 of Rubinstein, a fluorescent dye indicator dilution is measured using a one-dimensional photodetector, cf. column 5, lines 28-40. Such a photodetector is not capable of imaging. Rather, since only a concentration is to be measured in Rubinstein, only one light intensity is provided by the photodetector. *See* Rubinstein at for example, column 5, lines 41-49. Thus, the approach of Rubinstein, is not compatible with imaging nor is Rubinstein related to a distinct wavelength and, in particular, does not relate to light measurements concurrent with X-ray measurements. Rather, Rubinstein merely teaches clearance detection using light only, and, consequently, teaches away from the invention, which combines light imaging with X-ray imaging. Further, the device shown in Figure 1 and Figure 3 of Rubinstein is based on laser excitation which is inherently involved with emitting only one light point. Since only one light point is measured in Rubinstein, Applicants submit that the reference teaches away from any imaging methods. Thus, Applicants submit that Rubinstein lacks a teaching or suggestion to enable one of ordinary skill in the art to combine the reference with Combs or Nelson to arrive at the claimed invention.

In view of the foregoing, Applicant respectfully requests reconsideration and withdrawal of the outstanding rejection under § 103.

Claims 31-34 and 36-41

On pages 4-6 of the Office Action, the Office has rejected claims 31-34 and 36-41 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Combs in view of Nelson, further in view of Turner, further in view of Voirin, further in view of Rubinstein, and further in view of U.S. Patent No. 5,647,363 to Rabito *et al.* (hereafter "Rabito"). Applicants respectfully traverse this rejection for at least the reasons set forth below.

Applicant submits that Rabito fails to cure the deficiencies of Combs in view of Nelson, further in view of Turner, further in view of Voirin, and further in view of Rubinstein. Claims 31-34 and 36-41 ultimately depend from claim 29.

Applicants note that Rabito discloses a detector for detecting a clearance function and, consequently, does not provide any imaging method which would provide imaging data of the distribution of markers over a surface. It is clear from the structure presented in Figures 6 and 7 of Rabito that no imaging is envisaged (and thus imaging cannot be carried out with Rabito's device). Consequently, Rabito presents a device for measuring depletion of a detectable substance, cf. col. 2, lines 60-63. Therefore, Rabito relates to measuring of the mass or of a concentration of a substance within a detecting zone, in contrast to the invention which provides imaging.

Using the clearance detection of Combs with Rabito does not lead to the claimed invention. Rather, an apparatus would be defined by such a combination which allows to detect distinct X-ray photon energies and which provides only one intensity value for each X-ray energy which would reflect the concentration of the value active markers within the body. Since Combs teaches a clearance detection (and not an imaging system as defined in the invention), Combs teaches away from the invention. The combination of both prior art documents fails to show or render obvious to combine a light imaging detector and an imaging detector for radioactive substances.

In summary, at least Combs, Rubinstein as well as Rabito are related to methods and apparatuses for measuring clearance functions, that is, they are focused on the measurement of only one single intensity (and not an intensity distribution). Therefore, these documents teach away from any imaging method, in particular from the imaging method and apparatus as defined in the present claims. Nelson relates to X-ray imaging only and, consequently, does not show or render obvious any light detector system and, in particular, does not give any incentive for a person skilled in the art to combine the X-ray imaging of Nelson with light imaging. Particularly, the gratings shown in Figures 1 and 2 of Nelson are suited for X-rays only; since light can not be processed by these structures for obvious physical reasons, Nelson teaches away from any optical measurements.

Furthermore, Combs cannot be combined with Rabito. For example, Combs shows multimodal measurements of blood clearances using combined optical and radiometric

methods. As disclosed in column 6, lines 1-11 of Rabito, it is disclosed to detect clearance signals of optical and radiometric markers. In the context of single modality, Rabito is cited in column 4, lines 36-38. In column 8, lines 45-61, it is suggested to use a plurality of optical sensors at a tip of a catheter for detecting a number of distinct wavelengths of light. However, none of the device examples of Combs shows a combined detector for X-rays and light (even for measurements of intensities for one point only). Therefore, Combs suggests to use distinct, individual devices (for example, like shown in Rabito) for each detection mode. If devices according to Rabito are used, a first device would be placed at a first body part and a second, individual device would be placed at a second body part. However, these devices are only connected by the body and are not mutually connected. The resulting dislocation is not a problem when only assessing physiological functions like depletion. However, when assessing images with distinct systems, it would be critical to be able to combine the image data. In contrast to depletion measurements, the spatial arrangements of the detectors with regard to the object are vital to imaging detection. Therefore, Combs in combination with Rabito does not show or render obvious the arrangement of the invention. Rabito and Combs fail to show a multimodal imaging system comprised by a fixed arrangement of detectors of distinct kinds. Rather, Rabito and Combs are related to clearance measurements, and, consequently, teach away from the inventive imaging system.

In other words, the combination of Combs and Rabito would lead to the arrangement of two sleeves as shown in Rabito to the same person, the arrangement being capable for clearance measurements only. However, the present invention defines that the first and the second detector (at least the combination of the light detector and the radiomarker detector) are fixedly arranged in a specific spatial arrangement relative to each other. Since the combination of Combs and Rabito would lead to two individual sleeves arranged on the same arm, this combination of prior art does not show a fixed arrangement. Rather, it shows an indirect arrangement influenced by the movement of the object. Similar to a shoe and a wrist watch worn by the same person, two sleeves for aied according to Rabito worn by the same person or object can not be considered to be fixedly arranged.

Since, none of the additional references does anything to resolve the fundamental deficiencies in Combs, Applicant submits that no combination of these references can properly render either independent claim 29 or dependent claims 31-34 and 36-41 obvious. It

follows that if an independent claim is nonobvious under § 103, then any claim depending therefrom is nonobvious. *In re Fine*, 5 USPQ2d 1596 (Fed. Cir. 1988). See MPEP 2143.03. Thus, Applicants submit that claims 31-34 and 36-41, each of which ultimately depends from independent claim 29, is also non-obvious at least by virtue of their dependency from claim 29.

In view of the foregoing, reconsideration and withdrawal of the rejection are respectfully requested.

Claims 35

On pages 4-6 of the Office Action, the Office has rejected claim 35 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Combs in view of Nelson, further in view of Turner, further in view of Voirin, further in view of Rubinstein, further in view of Rabito, and further in view of U.S. Patent Application Publication 2002/0042566 to Matsuzaki *et al.* (hereafter “Matsuzaki”). Applicants respectfully traverse this rejection for at least the reasons set forth below.

Matsuzaki fails to cure the deficiencies of Combs in view of Nelson, further in view of Turner, further in view of Voirin, further in view of Rubinstein, and further in view of Rabito. As described above, Combs, Rubinstein as well as Rabito are related to methods and apparatuses for measuring clearance functions, that is, they are focused on the measurement of only one single intensity (and not an intensity distribution). Therefore, the references teach away from any imaging method, in particular from the imaging method and apparatus as defined in the present claims. Nelson relates to X-ray imaging only and, consequently, does not show or render obvious any light detector system and, in particular, does not give any incentive for a person skilled in the art to combine the X-ray imaging of Nelson with light imaging. Particularly, the gratings shown in Figures 1 and 2 of Nelson are suited for X-rays only; since light can not be processed by these structures for obvious physical reasons, Nelson teaches away from any optical measurements. Matsuzaki has only been applied here to teach using a position sensor. Regardless, whether Matsuzaki discloses or teaches a position sensor, or not, Applicants submit that Matsuzaki does not cure the fundamental deficiencies of the other references as described in depth above.

In view of the foregoing, reconsideration and withdrawal of the outstanding rejection are respectfully requested.

Additionally, if an independent claim is nonobvious under § 103, then any claim depending therefrom is nonobvious. *In re Fine*, 5 USPQ2d 1596 (Fed. Cir. 1988). See MPEP 2143.03. Thus, Applicant submit that claim 35, which ultimately depends from independent claim 29, is also non-obvious at least by virtue of their dependency from claim 29. Reconsideration and withdrawal of this rejection under § 103(a) are respectfully requested.

CONCLUSION

Applicant submits that the present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested.

The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by a check being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing or a credit card payment form being unsigned, providing incorrect information resulting in a rejected credit card transaction, or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicant hereby petitions for such extension under 37 C.F.R. § 1.136 and authorizes payment of any such extensions fees to Deposit Account No. 19-0741.

Respectfully submitted,

Date 9/24/09

By P.D.S.

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